

NDA 20-233/S-009

JUN 2 2000

AstraZeneca  
725 Chesterbrook Blvd  
Wayne, PA 19087-5677

Attention: Eric Couture, Ph.D.  
Director, Regulatory Liaison

Dear Dr. Couture:

Please refer to your supplemental new drug application dated August 26, 1999, received August 27, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rhinocort (budesonide) Nasal Inhaler.

We acknowledge receipt of your submission dated May 5, 2000. Your submission of May 5, 2000, constituted a complete response to our February 23, 2000 action letter.

This supplemental new drug application provides for a Geriatric Use subsection in the PRECAUTIONS section of the labeling.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted labeling (package insert submitted May 5, 2000).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-233/S-009." Approval of this submission by FDA is not required before the labeling is used.

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If a letter communicating important information about this drug product (i.e., a “Dear Health Care Practitioner” letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MED WATCH, HF-2  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Mrs. Gretchen Trout, Project Manager, at (301) 827-1058.

Sincerely yours,

Robert J. Meyer M.D.  
Director  
Division of Pulmonary and Allergy Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

# RHINOCORT®

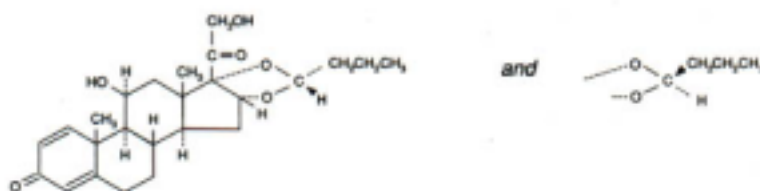
(budesonide) Nasal Inhaler

**For Intranasal Use Only.**

**Shake Well Before Use.**

## DESCRIPTION

Budesonide, the active component of Rhinocort® Nasal Inhaler, is an anti-inflammatory glucocorticosteroid. It is designated chemically as (RS)-11 $\beta$ ,16 $\alpha$ ,17,21-Tetrahydroxy- pregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S). The empirical formula of budesonide is C<sub>25</sub>H<sub>34</sub>O<sub>6</sub> and its molecular weight is 430.5. Its structural formula is:



Budesonide is a white to off-white odorless powder that is practically insoluble in water and in heptane, sparingly soluble in ethanol, and freely soluble in chloroform. Its partition coefficient between octanol and water at pH 7.4 is  $1.6 \times 10^3$ .

Rhinocort Nasal Inhaler is a metered-dose pressurized aerosol unit containing a suspension of micronized budesonide in a mixture of propellants, (dichlorodifluoromethane, trichloromonofluoromethane, and dichlorotetrafluoroethane) and sorbitan trioleate. Each actuation releases 50  $\mu$ g budesonide from the valve and delivers approximately 32  $\mu$ g budesonide from the nasal adapter (dose to patient). Throughout the package insert 32  $\mu$ g per actuation is used to calculate the dose administered. One canister provides at least 200 metered doses.

## CLINICAL PHARMACOLOGY

Budesonide is a glucocorticosteroid having a potent glucocorticoid and weak mineralocorticoid activity. In standard *in vitro* and animal models, budesonide has an approximately 200

fold higher affinity for the glucocorticoid receptor and a 1000 fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay.

The precise mechanism of glucocorticosteroid actions on allergic and nonallergic rhinitis is not known. Glucocorticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes and cytokines) involved in allergic and nonallergic/irritant-mediated inflammation.

Corticoids affect the delayed (6 hour) response to an allergen challenge more than the histamine-associated immediate response (20 minute). The clinical significance of these findings is unknown.

**Pharmacokinetics:** The pharmacokinetics of budesonide have been studied following nasal, oral and intravenous administration. Pharmacokinetic studies were performed with doses higher than those used clinically because at clinical doses the resulting plasma levels are below the limits of detection.

The results are as follows:

Route of Administration	Mean*[range]				
	T <sub>max</sub> (hr)	C <sub>max</sub> ** (nmol/L)	Systemic Availability***	V <sub>D</sub> (L)	Clearance (L/min)
Nasal Inhaler (N=9)	0.6[0.3-2]	0.52[0.24-0.88]	21[16-27]	–	–
Oral Capsule (N=11)	1.0[0.5-2]	0.33[0.19-0.50]	12[8-20]	–	–
I.V. (N=11)	–	–	100	201[102-275]	1.2[0.8-1.5]

\* mean of the two epimers

\*\* dose normalized to a 256 µg dose

\*\*\*% of delivered dose

Only about 20% of an intranasal dose from the Rhinocort Nasal Inhaler reaches the systemic circulation.

While budesonide is well absorbed from the GI tract, the oral bioavailability of budesonide is low (~10%) primarily due to extensive first pass metabolism in the liver. After reaching the systemic circulation, plasma levels decline in a log linear manner with an apparent elimination half-life of approximately 2 hours.

Budesonide has a volume of distribution of approximately 200 L and is 88% protein bound in the plasma. Budesonide is a mixture of two epimers, 22R and 22S. In glucocorticoid receptor affinity studies, the 22R form is two times as active as the 22S epimer. It

is also preferentially cleared by the liver with an apparent systemic clearance of  $1.4 \pm 0.3$  L/min., vs.  $1.0 \pm 0.2$  L/min. for the 22S form. *In vitro* studies indicate that the two forms of budesonide do not interconvert.

Budesonide is rapidly and extensively metabolized in man by the liver. *In vitro* studies looking at sites of metabolism showed negligible metabolism in skin, lung, and serum. After intranasal administration of a radiolabeled dose, 2/3 of the radioactivity was found in the urine and the remainder in the feces by 96 hours. The primary metabolites of budesonide in the urine following IV administration are 16 $\alpha$ -hydroxyprednisolone (24%) and 6 $\beta$ -hydroxybudesonide (5%). An additional 34% of the radioactivity recovered in the urine were conjugates. No unchanged budesonide was found in the urine. These results regarding the metabolic fate of budesonide parallel results obtained in *in vitro* metabolic studies using human liver homogenates.

*In vitro* studies of the binding of the two primary metabolites to the glucocorticoid receptor indicate that they have less than 1% of the affinity for the receptor as the parent compound budesonide.

**Pharmacodynamics:** The effect of Rhinocort Nasal Inhaler at a dosage of two sprays in each nostril morning and evening (total daily dose of 256  $\mu$ g) on hypothalamic-pituitary-adrenal (HPA) axis function has been evaluated in 275 adults and 61 children following short-term use (<2 months) and in 113 adults and 116 children following longer use (6–48 months). Early morning plasma cortisol and the short cosyntropin stimulation test (30–60 minutes) were the most commonly performed assessments of HPA function. Twenty-four hour urinary cortisol levels were determined in 50 adults (short term) and 96 children (long term). There were no statistically significant changes from baseline measurements in early morning plasma cortisol or 24-hour urinary cortisol excretion or in response to cosyntropin.

In a crossover trial using single doses of 200, 400 and 800  $\mu$ g of an aqueous formulation of budesonide administered intranasally at 10 P.M., a dose-dependent decrease in urinary cortisol excretion was found between 10 P.M. and 8 A.M. the following morning. The same study has not been performed with Rhinocort Nasal Inhaler. However, in a study using the Rhinocort Nasal Inhaler administered at 10 P.M., doses four (1024  $\mu$ g) and eight (2048  $\mu$ g) times higher than the recommended daily dose (256  $\mu$ g) were followed by a significant decrease in plasma cortisol levels at 8 A.M. the following morning (17% and 22%, respectively).

A 3 week clinical study in seasonal rhinitis, comparing Rhinocort

Nasal Inhaler and orally ingested budesonide with placebo in 98 patients with allergic rhinitis due to birch pollen, demonstrated that the therapeutic effect of budesonide can be attributed to the topical effects of budesonide. Intranasally, 128 µg of budesonide applied twice daily (55 µg systemically absorbed/day) provided clinically and statistically significant evidence of efficacy, whereas 250 µg of budesonide ingested twice a day as a capsule (65 µg systemically absorbed/day) was no different from placebo in reducing nasal symptoms.

**Clinical Trials:** The prophylactic and therapeutic efficacy of Rhinocort Nasal Inhaler has been evaluated in 20 controlled clinical trials of seasonal or perennial rhinitis. The number of patients treated with budesonide in these studies was 50 male and 33 female patients ages 6 to 12 years old, 77 males and 62 females ages 13 to 18 years old, 185 males and 246 females ages 19 to 64 and 1 male and 2 females over 64. The patients were predominantly caucasian.

Double-blind clinical trials of two to four weeks duration have shown that, compared with placebo, Rhinocort Nasal Inhaler 128 µg b.i.d. (two sprays in each nostril morning and evening) or 256 µg q.d. (four sprays in each nostril in the morning) provides statistically significant relief of nasal symptoms such as blockage, rhinorrhea, itching, and sneezing in adults and children with seasonal allergic rhinitis or perennial allergic rhinitis. Similar improvement has also been demonstrated in adults with nonallergic perennial rhinitis.

The therapeutic effect of Rhinocort Nasal Inhaler compared with placebo has been demonstrated by rhinoscopic examinations in children and adults with seasonal or perennial allergic rhinitis and adults with nonallergic perennial rhinitis. Biopsies of the nasal mucosa of 50 adult patients after 12 months of treatment and of 10 patients after 3–5 years of therapy showed no histopathological evidence of adverse effects. The clinical significance of either of these findings is unknown.

**Individualization of Dosage:** It is recommended that the starting dose for all adults be 256 µg daily, as either two sprays in each nostril twice per day, morning and evening, or as four sprays in each nostril once a day in the morning. The effect should be assessed 3–7 days after initiating treatment and then periodically until the patient's symptoms are stable. If adequate relief of symptoms is not achieved after 3 weeks of treatment, then Rhinocort Nasal Inhaler should be discontinued.

In patients who do achieve a good result it is desirable, once the maximum benefit seems to have been achieved, to titrate an individual patient to the minimum effective dose.

Because of the generally short duration of therapy for seasonal allergic rhinitis, it is usually not necessary to do this.

In patients with perennial allergic rhinitis, once adequate relief has been obtained the dose should be gradually decreased every 2–4 weeks as long as the desired clinical effect is maintained. If symptoms return, the dose may briefly be increased to the patient's starting dose and then returned to the dose the patient was on before symptoms reoccurred. As with other aerosolized nasal glucocorticosteroids, the vehicle used to deliver the glucocorticosteroid may cause symptoms that are difficult to distinguish from the patient's rhinitis symptoms. The corticoid may suppress symptoms caused by the vehicle at higher doses but as the dose is decreased symptoms from the vehicle may emerge. If a patient needs chronic treatment and the daily dose cannot be decreased from the starting dose, it may be advisable to try alternative therapy.

### **INDICATIONS AND USAGE**

Rhinocort Nasal Inhaler is indicated for the management of symptoms of seasonal or perennial allergic rhinitis in adults and children and nonallergic perennial rhinitis in adults. Rhinocort Nasal Inhaler is not recommended for treatment of nonallergic rhinitis in children because adequate numbers of such children have not been studied.

### **CONTRAINDICATIONS**

Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

### **WARNINGS**

The replacement of a systemic glucocorticosteroid with a topical glucocorticosteroid can be accompanied by signs of adrenal insufficiency, and in addition some patients may experience symptoms of withdrawal, e.g., joint and/or muscular pain, lassitude and depression. Patients previously treated for prolonged periods with systemic glucocorticosteroids and transferred to topical glucocorticosteroids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic glucocorticosteroid treatment, too rapid a decrease in systemic glucocorticosteroids may cause a severe exacerbation of their symptoms.

The use of Rhinocort Nasal Inhaler with alternate-day systemic prednisone could increase the likelihood of hypothalamic-pituitary-adrenal (HPA) suppression compared with a therapeutic dose of either one alone. Therefore, Rhinocort Nasal Inhaler should be used with caution in patients already receiving

alternate-day prednisone treatment for any disease. In addition, the concomitant use of Rhinocort Nasal Inhaler with other inhaled glucocorticosteroids could increase the risk of signs or symptoms of hypercorticism and/or suppression of the HPA-axis.

Patients who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on immunosuppressant doses of corticosteroids. In such children or adults, who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package insert for complete VZIG and IG prescribing information). If chicken pox develops, treatment with antiviral agents may be considered.

## **PRECAUTIONS**

**General:** Rarely, immediate hypersensitivity reactions or contact dermatitis may occur after the intranasal administration of budesonide. Rare instances of wheezing, nasal septum perforation and increased intraocular pressure have been reported following the intranasal application of aerosolized glucocorticosteroids.

Like other glucocorticosteroids, budesonide is absorbed into the circulation. Use of excessive doses of glucocorticosteroids may lead to signs or symptoms of hypercorticism, suppression of HPA function and/or suppression of growth in children or teenagers. In short term studies of the acute effect of inhaled budesonide 256 µg/day on lower leg growth (knemometry), it like other inhaled and intramuscular corticoids which have been studied showed a decrease in the rate of lower leg growth. The clinical significance of this finding is not known. In two one-year studies in 92 children taking recommended doses of Rhinocort Nasal Inhaler, height and skeletal stature were consistent with chronological age. Physicians should closely follow the growth of children taking corticoids, by any route, and weigh the benefits of corticoid therapy against the possibility of growth suppression if a child's growth appears slowed.

Although systemic effects have been minimal with recommended doses of Rhinocort Nasal Inhaler, this potential risk increases with larger doses. Therefore, larger than recommended doses of



Rhinocort Nasal Inhaler should be avoided.

When used at larger doses, systemic glucocorticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, the dosage of Rhinocort Nasal Inhaler should be discontinued slowly, consistent with accepted procedures for discontinuing oral glucocorticosteroid therapy.

In clinical studies with budesonide administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy and discontinuation of treatment with Rhinocort Nasal Inhaler. Patients using Rhinocort Nasal Inhaler over several months or longer should be examined periodically for evidence of *Candida* infection or other signs of adverse effects on the nasal mucosa.

Rhinocort Nasal Inhaler should be used with caution, if at all, in patients with active or quiescent tuberculous infections, untreated fungal, bacterial, or systemic viral infections, or ocular herpes simplex.

Because of the inhibitory effect of glucocorticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or nasal trauma should not use a nasal glucocorticosteroid until healing has occurred.

**Information for Patients:** Patients being treated with Rhinocort Nasal Inhaler should receive the following information and instructions.

Patients should use Rhinocort Nasal Inhaler as prescribed. A decrease in symptoms may occur as soon as 24 hours after starting glucocorticosteroid therapy and generally can be expected to occur within a few days of initiating therapy in allergic rhinitis. The patient should contact the physician if symptoms do not improve by three weeks, or if the condition worsens. Nasal irritation and/or burning after use of the spray occur only rarely with this product. The patient should contact the physician if they occur repeatedly.

Patients who are on corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, they should consult their physician without delay.

For the proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying patient instructions carefully.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** In a two-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in the male rats receiving an oral dose of 50 mcg/kg (approximately twice the maximum recommended daily intranasal dose in adults and children on a mcg/m<sup>2</sup> basis). No tumorigenicity was seen in male and female rats at respective oral doses up to 25 and 50 mcg/kg (approximately equal to and two times the maximum recommended daily intranasal dose in adults and children on a mcg/m<sup>2</sup> basis, respectively). In two additional two-year studies in male Fischer and Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 mcg/kg (approximately twice the maximum recommended daily intranasal dose in adults and children on a mcg/m<sup>2</sup> basis). However, in male Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (approximately twice the maximum recommended daily intranasal dose in adults and children on a mcg/m<sup>2</sup> basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) in these two studies showed similar findings.

In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 mcg/kg (approximately 3 times the maximum recommended daily intranasal dose in adults and children on a mcg/m<sup>2</sup> basis).

Budesonide was not mutagenic or clastogenic in six different test systems: Ames, *salmonella*/microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, sex-linked recessive lethal test in *Drosophila melanogaster*, and DNA repair analysis in rat hematocyte culture.

In rats, budesonide caused a decrease in prenatal viability and viability of the pups at birth and during lactation, along with a decrease in maternal body-weight gain, at subcutaneous doses of 20 mcg/kg and above (less than the maximum recommended daily intranasal dose in adults on a mcg/m<sup>2</sup> basis). No such effects were noted at 5 mcg/kg (less than the maximum recommended daily intranasal dose in adults on a mcg/m<sup>2</sup> basis).

**Pregnancy:** Teratogenic Effects: Pregnancy Category C: Budesonide was teratogenic and embryocidal in rabbits and rats. Budesonide produced fetal loss, decreased pup weights, and skeletal abnormalities at subcutaneous doses of 25 mcg/kg in rabbits and 500 mcg/kg in rats (approximately 2 and 16 times the

maximum recommended daily intranasal dose in adults on a mcg/m<sup>2</sup> basis).

In another study in rats, no teratogenic or embryocidal effects were seen at inhalation doses up to 250 mcg/kg (approximately 8 times the maximum recommended daily intranasal dose in adults on a mcg/m<sup>2</sup> basis, respectively).

No changes were seen at subcutaneous doses of 5 mcg/kg and 100 mcg/kg in rabbits and rats, respectively (less than and approximately 3 times the maximum recommended daily intranasal dose in adults on a mcg/m<sup>2</sup> basis, respectively). In another study in rats, no teratogenic or embryocidal effects were seen at inhalation doses up to 250 mcg/kg (approximately 8 times the maximum recommended daily intranasal dose in adults on mcg/m<sup>2</sup> basis).

There are no adequate and well-controlled studies in pregnant women. Budesonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral glucocorticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from glucocorticosteroids than humans. In addition, because there is a natural increase in glucocorticosteroid production during pregnancy, most women will require a lower exogenous glucocorticosteroid dose and many will not need glucocorticosteroid treatment during pregnancy.

**Nonteratogenic Effects:** Hypoadrenalism may occur in infants born of mothers receiving glucocorticosteroids during pregnancy. Such infants should be carefully observed.

**Nursing Mothers:** It is not known whether budesonide is excreted in human milk. Because other glucocorticosteroids are excreted in human milk, caution should be exercised when Rhinocort Nasal Inhaler is administered to nursing women.

**Pediatric Use:** Safety and effectiveness in children below 6 years of age have not been established. Oral glucocorticosteroids have been shown to cause growth suppression in children and teenagers with extended use. If a child or teenager on any glucocorticosteroid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of glucocorticosteroids should be considered (see PRECAUTIONS).

**Geriatric Use:** Clinical studies of Rhinocort Nasal Inhaler did not

include a sufficient number of patients 65 years of age and older to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in either clinical safety or efficacy between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

## ADVERSE REACTIONS

Adverse reaction information is derived from blinded-controlled clinical trials (see Clinical Trials), open label studies and marketing experience. In the description below, rates of rare events are derived principally from marketing experience and publications, and accurate estimates of incidence are not possible.

The incidence of common adverse reactions is based upon controlled clinical trials in 606 patients [101 girls and 145 boys (<19 years of age) and 203 female and 157 male adults] treated with Rhinocort Nasal Inhaler 128 µg twice daily over 2–4 weeks. The most common adverse reactions were symptoms of irritation of the nasal mucous membranes. All common adverse reactions were reported with approximately the same frequency by placebo patients suggesting the possibility that the vehicle or the rhinitis itself was responsible for the symptoms. Sneezing after use of the inhaler occurred in 2% of Rhinocort treated patients and in 11% of patients using the placebo.

Systemic glucocorticosteroid side-effects were not reported during controlled clinical studies with Rhinocort Nasal Inhaler. If recommended doses are exceeded, however, or if individuals are particularly sensitive, symptoms of hypercorticism, i.e., Cushing's syndrome, could occur.

### **Incidence Greater than 1% (Based on controlled clinical trials):**

Respiratory: nasal irritation\*, pharyngitis\*, cough increased\*, epistaxis\*.

Digestive: dry mouth, dyspepsia.

\*incidence 3 to 9%; incidence of unmarked reactions 1 to 3%.

### **Incidence Less than 1% (Based on controlled clinical trials):**

Respiratory: dyspnea, moniliasis, hoarseness, wheezing, nasal pain.

Special Senses: reduced sense of smell, bad taste.

Digestive: nausea.

Skin and Appendages: facial edema, rash, pruritus, herpes simplex.

Nervous System: nervousness.

Musculoskeletal: myalgia, arthralgia.

**Adverse Event Reports from Other Sources:** Rare adverse events reported in the published literature or from marketing experience include: immediate and delayed hypersensitivity reactions including rash, contact dermatitis, urticaria, angioedema, and bronchospasm; nasal septal disorders including atrophy, necrosis and/or perforation; symptoms of hypocorticism and hypercorticism; alopecia; psychiatric symptoms including depression, aggressive reactions, irritability, anxiety and psychosis.

## **OVERDOSAGE**

Acute overdosage with this dosage form is unlikely since one canister of Rhinocort Nasal Inhaler only contains approximately 12.7 mg of budesonide. Chronic overdosage may result in signs/symptoms of hypercorticism (see WARNINGS and PRECAUTIONS).

## **DOSAGE AND ADMINISTRATION**

Adults and children 6 years of age and older: The recommended starting dose is 256 µg daily, given as either two sprays in each nostril morning and evening or as four sprays in each nostril in the morning.

A decrease in symptoms may occur as soon as 24 hours after onset of treatment with Rhinocort Nasal Inhaler but generally it takes 3–7 days to reach maximum benefit.

If no improvement has been obtained by the third week of treatment with Rhinocort Nasal Inhaler, treatment should be discontinued.

After the desired clinical effect has been obtained, the maintenance dose should be reduced to the smallest amount necessary for control of symptoms (see Individualization of Dosage, CLINICAL PHARMACOLOGY section).

If glucocorticosteroids are discontinued when they still are needed, symptoms may not recur for several days.

At recommended doses, Rhinocort's therapeutic effects are localized to the nose, therefore, concomitant treatment may be necessary to counteract allergic eye symptoms. Doses exceeding 256 µg daily (4 sprays/nostril) are not recommended. Rhinocort Nasal Inhaler is not recommended for children below 6 years of age or for children with nonallergic perennial rhinitis because adequate numbers of these children have not been studied.

**Directions for Use:** Illustrated Patient's Instructions for Use

accompany each package of Rhinocort Nasal Inhaler.

### HOW SUPPLIED

Rhinocort Nasal Inhaler is supplied in a 7.0 g canister containing 200 metered doses provided with a metering valve and nasal adapter together with Patient's Instructions for Use. Each actuation delivers approximately 32 µg of micronized budesonide from the nasal adapter to the patient.

**R**only. Rhinocort Nasal Inhaler should be stored between 15°C (59°F) and 30°C (86°F) with the valve up. Shake well before use.

Each inhaler with actuator is packaged in an aluminum foil pouch to protect the product from moisture. After opening the aluminum pouch, the product should be used within 6 months and storage in an area of high humidity should be avoided.

**Contents under pressure.** Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 50°C (120°F) may cause the canister to explode. Never throw the container into fire or an incinerator. Keep out of reach of children.

**Note:** The indented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFCs).

**WARNING:** Contains trichloromonofluoromethane, dichlorotetrafluoroethane, and dichlorodifluoromethane, substances which harm public health and environment by destroying ozone in the upper atmosphere.

A notice similar to the above WARNING has been placed in the patient information leaflet of this product pursuant to EPA regulations.

Manufactured for:

**ASTRA**<sup>®</sup> Astra USA, Inc.  
Westborough, MA 01581